HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 March 09.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2014 November 01; 67(3): 304–309. doi:10.1097/QAI.0000000000000304.

Management of Fever in Ambulatory HIV-Infected Adults in Resource-Limited Settings: Prospective Observational Evaluation of a New Mozambican Guideline

Paula E. Brentlinger, MD, MPH[*], **Wilson P. Silva, PhD**[*,‡], **Manuel Buene, BS**[*], **Luis Morais, MS**[*], **Emilio Valverde, MD, PhD**[*], **Sten H. Vermund, MD, PhD**[*,†], and **Troy D. Moon, MD, MPH**[*,†]

[*]Friends in Global Health, LLC, Maputo, Mozambique

[†]Department of Pediatrics, Vanderbilt University, Nashville, TN

[‡]Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN

Abstract

A new Mozambican guideline for management of fever in HIV-infected adults requires malaria testing and systematic consideration of specific alternative diagnoses (eg, tuberculosis and bacterial infections) in addition to malaria. We conducted a prospective observational study of the guideline's performance. Of 258 HIV-infected subjects with axillary temperature ≥37.5° C or history of fever, 76.0% improved, 13.6% died or were hospitalized, and 10.5% were lost to follow-up. In multivariate analyses, factors associated with adverse outcomes were bacterial blood stream infection, syndromically diagnosed tuberculosis, lower $CD4^+$ T-lymphocyte count, no antiretroviral therapy, lower body mass index, lower hemoglobin, and nonprescription of antibiotics.

Keywords

fever; HIV/AIDS; Mozambique; guidelines; validation; syndromic diagnosis

BACKGROUND

Fever is common in HIV-infected adults in sub-Saharan Africa; its observed incidence was 602.5/1000 person-years in one Kenyan cohort.[1] The differential diagnosis of fever is broader in the HIV-infected adults and includes bacterial, mycobacterial, viral, parasitic, and fungal infections, adverse drug reactions, and malignancy.[2–4] Health workers in resource-

Correspondence to: Paula E. Brentlinger, MD, MPH, Vanderbilt Institute for Global Health, 2525 West End Avenue, Suite 750, Nashville, TN 37203 (brentp2@u.washington.edu).

Presented in part at the 20th Conference on Retroviruses and Opportunistic Infections, May 3–6, 2013, Atlanta, GA, Abstract #876.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the National Institutes of Health.

Conception and design: P.E.B., T.D.M., W.P.S., E.V., S.H.V.; acquisition of data: P.E.B., M.B., T.D.M., L.M., W.P.S., E.V.; analysis and interpretation of data: P.E.B., T.D.M., W.P.S., E.V.; drafting of manuscript: P.E.B., T.D.M., S.H.V.; and critical revision and approval of manuscript: All.

limited areas must often address this complex differential diagnosis with strictly syndromic guidelines.[5] One such guideline, from the Integrated Management of Adolescent and Adult Illness strategy, recommends presumptive antimalarials for all with fever or history of fever in malaria-endemic regions, with consideration of antibiotics, glucose, and tuberculosis (TB) and HIV evaluation only under certain circumstances.[6]

Mozambique, a resource-limited country,[7] adopted the acute care guideline of Integrated Management of Adolescent and Adult Illness for nonphysician clinicians managing fever in adults and adolescents. However, the guideline conflicted with the Mozambican Ministry of Health (MISAU) requirements for malaria testing before antimalarial treatment,[8] and MISAU became concerned about underdiagnosis of common HIV-associated causes of fever. MISAU subsequently revised the guideline for use in HIV/AIDS care. The new version required a more comprehensive medical history (including TB screening questions) and physical examination, malaria testing, and broader consideration of antibiotics. However, because causes of fever are rarely diagnosed etiologically at under-capacitated Mozambican peripheral health units, the new guideline (disseminated in 2009) was based largely on syndromic assessments.

We conducted a study (NCT 01681914, www.clinicaltrials.gov) to describe the new fever guideline's performance under Mozambican field conditions. The primary objectives were to measure (1) the proportion of febrile, ambulatory, HIV-infected adult patients who could be assigned an etiologic or syndromic diagnosis through application of the new guideline and (2) the proportion whose fevers improved with guideline-determined treatment.

METHODS

This prospective observational study was conducted in 3 health centers in Zambézia Province, Mozambique; its methods have been previously described.[9] Briefly, ambulatory HIV-infected adults ≥18 years old with axillary temperature ≥37.5° C or history of fever (preceding 24 h) were eligible. Patients were ineligible if rapid preliminary evaluation detected guideline-determined danger signs or if unable to communicate in Portuguese or Echuabo (a local language). Random selection was not logistically feasible.

At enrollment, clinical evaluation included rapid assessment for prespecified danger signs, medical chart review, standardized history (including TB screening questions), and physical examination. Laboratory evaluation (previously described)[9] included rapid antigen testing for *Plasmodium falciparum* malaria, rapid hemoglobin testing, and 1 set of bacterial blood cultures. Blood cultures were ordinarily unavailable in Zambézia Province and were strictly a study procedure. HIV testing, $CD4^+$ T-lymphocyte (CD4) count, sputum microscopy for TB, complete blood counts, and certain blood chemistries could be requested at clinician discretion and were available through the local or provincial hospital laboratories.

Study clinicians (Mozambican nonphysician clinicians) assigned etiologic and/or syndromic diagnoses for causes of fever and developed treatment plans. If not hospitalized, subjects were asked to return in 7 days or sooner if there were complications. At follow-up, subjects

were discharged if fever had resolved. If unimproved, subjects were scheduled for further visits until reaching a study end point.

Predefined end points (previously described)[9] were hospitalization, death, improvement of fever (or history thereof), or loss to follow-up (LTFU). Community outreach workers visited subjects at home if blood cultures were positive or if patients defaulted, unless subjects refused. Physician–investigators provided on-site supervision, including direct observation of clinician/patient encounters. We sought to enroll 324 subjects; our sample size estimates have been previously described.[9]

Statistical analyses were conducted in Stata 11.2 (Stata Corporation, College Station, TX). Etiologic diagnoses were limited to blood culture–confirmed bacteremia, smear-positive pulmonary TB, and malaria by rapid antigen test. Syndromic diagnoses were based on clinicians' application of Mozambican guidelines. We defined diagnosis of "specific fever focus" as clinician identification of a likely fever source linked to a single organ system (eg, pneumonia, pelvic inflammatory disease, or varicella zoster). Syndromic diagnoses of "suspected bacteremia" or "suspected bacterial infection (not otherwise specified)" were not considered indicative of localized fever foci.

We described subjects' baseline characteristics with proportions or medians with interquartile ranges. To describe associations between outcomes and subject characteristics, we used bivariate and multivariable logistic regressions. The composite adverse dependent outcome included death or hospitalization; patients with unknown outcomes were excluded.

The study protocol was approved by the Mozambican National Bioethics Committee and Vanderbilt University's Institutional Review Board. Study coordinators obtained informed consent (written or witnessed oral consent) at enrollment.

RESULTS

Recruitment occurred from May–August 2012. Enrollment was truncated at 258 subjects because of administrative deadlines and limited incubator capacity. The subjects' characteristics at enrollment are described in Table 1.

At enrollment, 13 subjects (5.0%) were hospitalized, and clinicians assigned 421 etiologic or syndromic diagnoses of fever. At least one localized fever focus was detected in 149 [57.8%, 95% confidence interval (CI): 51.5 to 63.9] subjects; the most common were acute respiratory infection [95 (36.8%)], suspected TB [74 (28.7%)], and malaria [38 (14.7%)]. The most frequently assigned diagnosis was presumed bacteremia [138 (53.5%)], often given to subjects with signs or symptoms implicating multiple organ systems: 2 or more in 135 (97.8%) and 3 or more in 106 (76.8%). Only 41 (15.9%) subjects acquired etiologic diagnoses (malaria or smear-positive pulmonary TB) at enrollment.

Of 245 subjects not hospitalized at enrollment, 46 (18.8%) received antimalarials and 220 (89.8%) antibiotics. The 11 subjects not prescribed antibiotics or antimalarials were diagnosed with herpes zoster (3), suspected TB (1), uncomplicated upper respiratory infection (1), oral candida (1), and no diagnosis (5).

Of 38 subjects with malaria antigenemia at enrollment, 32 (84.2%) had slide-confirmed parasitemia, 1 (2.6%) had negative microscopy, and 5 (13.2%) had no result because of reagent stockouts. Nine others with negative tests were prescribed antimalarials.

Of 258 sets of blood cultures drawn at enrollment, 39 (15.1%, 95% CI: 11.0 to 20.1) yielded pathogens (previously described).[9] Briefly, 32 (82.9%) were nontyphoid *Salmonella* (NTS), largely resistant to multiple first-line antibiotics. Of 4 *Streptococcus pneumoniae* isolates, 2 (50%) were resistant to penicillin and 1 (25%) to erythromycin. Most bacteremic subjects [26 (66.7%)] reported both gastrointestinal and respiratory symptoms. At enrollment, 5 (12.8%) were hospitalized, 17 (43.6%) were prescribed antibiotics for presumed bacteremia, and 11 (28.2%) were prescribed antibiotics for other conditions. Of 31 subjects with drug-resistant NTS or *S. pneumoniae* bacteremia, 10 required hospitalization (5 at enrollment and 5 after failure of ineffective antibiotics prescribed at enrollment). Of the 21 remaining subjects, 18 were prescribed effective antibiotics (predominantly ciprofloxacin) at enrollment and 3 subsequently required switching to effective antibiotics.

At study visit 2, 220 (89.8%) of 245 patients not hospitalized at enrollment were reevaluated. Most [186 (84.9%)] had improved, but 11 (5.0%) were hospitalized, and 23 (10.5%) were still symptomatic though ambulatory. Bacteremia and/or TB-related concerns were associated with most hospitalizations and failures to improve. One additional patient died (cause unknown) before the second visit.

After visit 2, 5 additional adverse outcomes occurred. Two deaths before study discharge were associated with treatment nonadherence and very late diagnosis of HIV/AIDS, respectively. Two deaths and 1 hospitalization occurred after improvement of fever: 1 death associated with progressively worsening anemia of unknown etiology after apparent recovery from *Escherichia coli* bacteremia, 1 death of unknown cause, and 1 hospitalization for recurrent fever with respiratory distress.

Before study initiation, the study clinicians had no experience with bacteremia. After the first 15 cases (80% NTS) were identified, antibiotic prescription increased from 56/76 subjects (73.7%) to 167/182 (91.8%, $P < 0.001$) at enrollment and shifted from usual first-line agents (eg, amoxicillin) to ciprofloxacin and azithromycin.

Ultimately, 196 (76.0%) subjects improved by visit 4 and 35 (13.6%) were hospitalized or died. The remaining 27 (10.5%) were LTFU. Only 82 (31.8%) ever acquired etiologic diagnoses, including 8 with confirmed malaria/NTS, TB/malaria, or TB/bacteremia coinfection.

For subjects not LTFU, lower or missing CD4, lower hemoglobin, lower body mass index, weight loss, esophageal candidiasis, syndromically diagnosed TB, and confirmed bacteremia were significantly associated with the composite adverse outcome by logistic regression (Table 2). Adjustment for interaction between bacteremia and antibiotic use attenuated the association between bacteremia and adverse outcomes [odds ratio (OR) = 0.71, 95% CI: 0.11 to 4.48, if antibiotics were prescribed at the initial visit]. Even in the absence of bacteremia, antibiotics were protective (OR = 0.54, 95% CI: 0.30 to 1.00). The OR for association with adverse outcomes was highest for patients with CD4 <350 cells per

microliter who were not on antiretroviral therapy (ART) (OR = 11.86, 95% CI: 7.18 to 19.59) as compared with patients with higher CD4 counts (reference category). The OR for association of smear-positive pulmonary TB and adverse outcomes was undefined because no subjects with smear-positive TB had adverse outcomes.

DISCUSSION

Nonphysician clinicians, using a largely syndromic Mozambican fever guideline, identified specific probable foci of fever in 149 (57.8%) HIV-infected adult subjects at enrollment, and the lower limit of the 95% CI (51.5%) exceeded the 50% threshold considered in our sample size[9] calculations. Only 46 subjects (17.8%) were treated for malaria, 37 of whom (80.4%) had positive malaria tests, thus avoiding unnecessary malaria treatment in the majority and supporting Mozambique's malaria testing policy.

Although fewer than 60% of subjects acquired diagnoses associated with specific fever foci at enrollment, nearly 90% of subjects not hospitalized were prescribed antibiotics. Antibiotic prescription may have been prompted by high symptom burdens, high prevalence of respiratory symptoms suggesting bacterial pneumonia, or by concern that failure to prescribe effective antibiotics might result in clinical deterioration of bacteremic subjects before receipt of blood culture results.

Encouragingly, 186 (84.6%) of 220 subjects seen in follow-up had improved by visit 2 and were discharged from the study, but it is unclear without counterfactual evidence whether the guideline's recommendations actually caused the observed improvement in those without laboratory-confirmed malaria or TB.

Without blood cultures, antimicrobial susceptibility testing, and active tracing (all study, not routine, procedures), all 31 subjects with drug-resistant bacteremia would probably have been treated ineffectively with first-line antibiotics. Had all required hospitalization, observed adverse outcomes would have increased by more than 50%.

In subjects without confirmed bacteremia, antibiotics may still have been beneficial. The sensitivity of blood cultures may be less than 40%.[10,11] If this estimate is generalizable to our subjects, the true number with bacteremia that responded to antibiotics may have been higher. Then again, if viral etiologies of acute respiratory infection were as common as has been reported elsewhere, overprescription of antibiotics may have been substantial.[12,13] Based on the available evidence, we are unable to determine which individual subjects had blood culture–negative bacterial infections responsive to presumptive antibiotics vs. spontaneous resolution of viral infections.

Both delayed evaluation of TB suspects and presumptive diagnosis of smear-negative TB were associated with initial management failure and/or adverse outcomes. This may reflect late diagnosis of genuine TB or persistent TB-like pulmonary symptoms actually caused by other opportunistic diseases that could not be diagnosed locally. Untreated AIDS was also significantly associated with poor outcomes.

Because our sample was nonrandom, the 95% CIs around our point estimates must be interpreted cautiously. Our findings are likely generalizable to other Mozambican settings, though, because malaria and TB are present nationwide, late ART initiation is common, and drug-resistant NTS has been described in southern Mozambique and neighboring Malawi.[14–16]

Although the majority of subjects improved, nearly 1 in 7 had adverse outcomes, etiologic diagnoses were confirmed in fewer than one-third, potentially fatal bacteremia diagnoses would have been missed in more than one-sixth without blood cultures (largely unavailable in Mozambique), and the combination of high symptom burdens and limited diagnostic capacity often precluded identification of a single fever cause. Overprescription of antibiotics may have succeeded overprescription of antimalarials as a management error, but the exact magnitude of overprescription is uncertain because the proportion of blood culture–negative patients who did have bacterial infections is unknown.

Our findings do not support the assumption that malaria testing, focused history, and physical examination will correctly identify a single unique fever focus in HIV-infected patients.

Possible strategies for improvement of guideline performance might include the following: enhanced microbiologic surveillance, improved access to rapid TB testing, evidence-based guidelines for presumptive antibiotic prescription, consistent restaging of febrile HIV-infected patients, guidance for prioritization of interventions in patients with multiple signs/symptoms, and revision of danger sign criteria. Clinical and operational research, aggressive scale-up of existing interventions, and more timely ART initiation will be required to further this life-saving agenda.

Acknowledgments

The authors thank the study subjects for their participation. Members of the study team included the following: Jorge Fernandes Baulene, Maria Joaquina Arnaldo Chipendane, Carlos Domingos, Roque Pinto Azevedo Oliveira (site coordinators); António Fernando Ditone Macule, Atanásio Monteiro Fiscal, Marcelina Vicente Vatiua, Vidigal José Chaque, Francisco Basilio Malumbia, Elias Pedro Amade, Lorena Onofre Gonçalves (study clinicians); Gilberto Ali Ussene, Carlitos Goveia Pequenino (community outreach); Rui Cipriano Colofite, Oscar Antonio, Argélio Armando Lubulino Onofre, Fernando Zita, Adelina Damas, Fernando Vilanculos (laboratory); and Carmelinda Rocha, Menezes Domingos Madeira (data entry). Others who provided invaluable support for study design or implementation or Mozambican guideline development included the following: Massada da Rocha, Moises Daniel Sitoi, Juma Azarate Jahar, Ligia Esther Bandera Elizastigui, Virginia Saldanha, the District Health Directorates of Inhassunge and Namacurra, the City Health Directorate of Quelimane, the Provincial Health Directorate of Zambézia Province, the clinical, nursing, and counseling staff of the participating health centers, Rui Bastos, Rolanda Manuel, Alberto Baptista, Mohsin Sidat, Bill Wester, Lisa Nelson, Marcia Souza, Mark Micek, Paul Thottingal, I-TECH’s curriculum development team (especially José Vallejo Torres, Pilar Martínez Martínez, Mónica Negrete, Florindo Martins Mudender, and María Ruano Camps), MISAU’s Therapeutics Committee (Comité Terapéutico), Meredith Blevins, and Alfredo Vergara.

Supported by the President’s Emergency Plan for AIDS Relief through the Centers for Disease Control and Prevention under the terms of Cooperative Agreement U2GPS000631 to Vanderbilt University. The REDCap (Research Electronic Data Capture; http://www.project-redcap.org/) online database that we used for initial data entry and management was supported by grant number UL1 TR000445 from NCATS/NIH.

References

1. Mwachari CW, Shepherd BE, Cleopa O, et al. Mortality and burden of disease in a cohort of HIV-seropositive adults in Nairobi, Kenya. Int J STD AIDS. 2004; 15:120–126. [PubMed: 15006075]
2. Anglaret X, Dakoury-Dogbo N, Bonard D, et al. Causes and empirical treatment of fever in HIV-infected adult outpatients, Abidjan, Cote d'Ivoire. AIDS. 2002; 16:909–918. [PubMed: 11919493]
3. Van Oosterhout JJ, Laufer MK, Graham SM, et al. A community-based study of the incidence of trimethoprim-sulfamethoxazole-preventable infections in Malawian adults living with HIV. J Acquir Immun Defic Syndr. 2005; 39:626–631.
4. World Health Organization. WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease. Geneva, Switzerland: WHO Press; 2006.
5. Crump JA, Gove S, Parry CM. Management of adolescents and adults with febrile illness in resource limited areas. BMJ. 2011; 343:d4847. [PubMed: 21824901]
6. World Health Organization. Interim Guidelines for First-level Facility Health Workers at Health Centre and District Outpatient Clinics. Geneva, Switzerland: World Health Organization; 2004. Integrated Management of Adolescent and Adult Illness.
7. United Nations Development Programme. International Human development Indicators. Available at: http://hdrstats.undp.org/en/countries/profiles/MOZ.html. Accessed June 14, 2014
8. República de Moçambique. Ministério da Saúde. Direcção Nacional de Saúde Pública. Programa Nacional de Controlo da Malária. Inquérito Nacional Sobre Indicadores de Malária em Moçambique (IIM-2007). Maputo, Mozambique: Ministério da Saúde; 2009.
9. Moon TD, Silva WP, Buene M, et al. Bacteremia as a cause of fever in ambulatory, HIV-infected Mozambican adults: results and policy implications from a prospective observational study. PloS One. 2013; 8:e83591. [PubMed: 24386229]
10. Westh H, Lisby G, Breysse F, et al. Multiplex real-time PCR and blood culture for identification of bloodstream pathogens in patients with suspected sepsis. Clin Microbiol Infect. 2009; 15:544–551. [PubMed: 19392905]
11. Tsalik EL, Jones D, Nicholson B, et al. Multiplex PCR to diagnose bloodstream infections in patients admitted from the emergency department with sepsis. J Clin Microbiol. 2010; 48:26–33. [PubMed: 19846634]
12. Feikin DR, Njenga MK, Bigogo G, et al. Etiology and incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007–2010. PloS One. 2012; 7:e43656. [PubMed: 22937071]
13. Nduba VN, Mwachari CW, Magaret AS, et al. Placebo found equivalent to amoxicillin for treatment of acute bronchitis in Nairobi, Kenya: a triple blind, randomised, equivalence trial. Thorax. 2008; 63:999–1005. [PubMed: 18559367]
14. Lahuerta M, Lima J, Nuwagaba-Biribonwoha H, et al. Factors associated with late antiretroviral therapy initiation among adults in Mozambique. PloS One. 2012; 7:e37125. [PubMed: 22615917]
15. Mandomando I, Sigauque B, Morais L, et al. Antimicrobial resistance trends of bacteremia isolates in a rural hospital in southern Mozambique. Am J Trop Med Hyg. 2010; 83:152–157. [PubMed: 20595494]
16. Gordon MA, Graham SM, Walsh AL, et al. Epidemics of invasive *Salmonella enteriditis* serovar Enteriditis and *S. typhimurium* infections among adults and children, associated with multidrug resistance in Malawi. Clin Infect Dis. 2008; 46:963–969. [PubMed: 18444810]

TABLE 1

Characteristics of Fever Study Subjects at Enrollment (Study Visit 1), Overall and by Study Outcome

Patient Characteristic, n (%) or Median (Interquartile Range)	All Subjects (n = 258)	Study End Points		
		Improved (n = 196)	Hospitalized or Died (n = 35)	LTFU (n = 27)
Demographics				
Site				
Coalane	77 (29.8)	60 (30.6)	9 (25.0)	8 (29.6)
Inhassunge	94 (36.4)	70 (35.7)	13 (37.1)	11 (40.7)
Namacurra	87 (33.7)	66 (33.7)	13 (37.1)	8 (29.6)
Gender, pregnancy status				
Pregnant	11 (4.3)	8 (4.1)	1 (2.9)	2 (7.4)
Female, nonpregnant	163 (63.2)	127 (64.8)	19 (54.3)	17 (63.0)
Male	84 (32.6)	61 (31.1)	15 (42.9)	8 (29.6)
Age (yrs)	30 (25–38)	30 (25–38)	33 (27–40)	30 (25–36)
Illiterate	113 (43.8)	80 (40.8)	19 (54.3)	14 (51.9)
Did not permit home visits	13 (5.0)	7 (3.6)	1 (2.9)	5 (18.3)
HIV/AIDS status				
Current CD4 (cells/μL) * (65 missing)	225 (93–434)	254.5 (99–458.5)	134 (91–221)	194 (55–480)
CD4 (cells/μL), categories				
<200	89 (34.5)	61 (31.1)	18 (51.4)	10 (37.0)
200–349	37 (14.3)	30 (15.3)	6 (17.1)	1 (3.7)
350–499	30 (11.6)	24 (12.2)	1 (2.9)	5 (18.5)
≥500	37 (14.3)	33 (16.8)	1 (2.9)	3 (11.1)
None available	65 (25.2)	48 (24.5)	9 (25.7)	8 (29.6)
Co-trimoxazole prophylaxis	170 (65.9)	136 (69.4)	19 (54.3)	15 (55.6)
ART	91 (35.3)	75 (38.3)	9 (25.7)	7 (25.9)
Eligible for ART but not on treatment	106 (41.1)	73 (37.2)	22 (62.9)	11 (40.7)
Vital signs				
Axillary temperature (°C)	37.6 (37.2–38.2)	37.6 (37.2–38.2)	37.7 (37.4–38.7)	37.5 (37.2–38.6)
Body mass index (kg/m^2) (6 missing)	19.5 (17.5–21.3)	19.8 (17.7–21.5)	18.0 (16.5–18.9)	19.1 (17.2–21.3)
Hemoglobin				
Hemoglobin (g/dL) (2 missing)	10.3 (8.8–12.0)	10.7 (9.0–12.5)	9.0 (7.4–10.5)	9.5 (8.5–10.8)
Comorbidities				
Peripheral neuropathy	2 (0.8)	2 (1.0)	0	0
Sexually transmitted infection (excludes pelvic inflammatory disease)	14 (5.4)	11 (5.6)	2 (5.7)	1 (3.7)
Oral candidiasis	14 (5.4)	9 (4.6)	4 (11.4)	1 (3.7)
Suspected esophageal candidiasis	7 (2.7)	3 (1.5)	3 (8.6)	1 (3.7)
Cutaneous mycosis	6 (2.3)	5 (2.6)	1 (2.9)	0
Suspected Kaposi sarcoma	5 (1.9)	5 (2.6)	0	0
Active TB not yet diagnosed by clinician (discovered later in study)	20 (7.8)	13 (6.6)	4 (11.4)	3 (11.1)

Patient Characteristic, n (%) or Median (Interquartile Range)	All Subjects (n = 258)	Study End Points		
		Improved (n = 196)	Hospitalized or Died (n = 35)	LTFU (n = 27)
Symptoms				
Cough	178 (69.0)	136 (69.4)	25 (71.4)	17 (63.0)
Any upper respiratory symptom (sore throat, sneezing, congestion, ear pain)	181 (70.2)	135 (68.9)	23 (65.7)	23 (85.2)
Any lower respiratory symptom (dyspnea, chest pain, hemoptysis)	172 (66.7)	128 (65.3)	26 (74.3)	18 (66.7)
Any gastrointestinal symptom (nausea, vomiting, diarrhea, abdominal pain)	155 (60.1)	117 (59.7)	22 (62.9)	16 (59.3)
Any genitourinary symptom (discharge, dysuria, ulcer)	56 (21.7)	39 (19.9)	12 (34.3)	5 (18.5)
Headache	214 (83.0)	164 (83.7)	27 (77.1)	23 (85.2)
Skin problems (rash, lymphadenopathy)	18 (7.0)	14 (7.1)	3 (8.6)	1 (3.7)
Weight loss	74 (28.7)	48 (24.5)	19 (54.3)	7 (25.9)

* Results from testing ≤6 months before enrollment or after enrollment if no reported CD4 count result in the preceding 6 months.

TABLE 2

Bivariate and Multivariable Correlations Between Subject Characteristics at First Study Visit and Study Outcome

Subject Characteristics at First Study Visit (n = 231 Subjects Who Improved, Died, or Were Hospitalized; Subjects With Unknown Outcomes Were Excluded)	Bivariate Associations With Death or Hospitalization (n = 231)		Multivariable Associations With Death or Hospitalization, Adjusted for Presumed Correlation of Outcomes Within Sites (n = 224)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographics				
Site				
Coalane	Reference	—	—	—
Inhassunge	1.24 (0.49 to 3.10)	0.648	—	—
Namacurra	1.31 (0.52 to 3.29)	0.561	—	—
Gender, pregnancy status				
Pregnant	0.84 (0.10 to 7.06)	0.869	—	—
Female, nonpregnant	Reference	—	—	—
Male	1.64 (0.78 to 3.45)	0.190	—	—
Age (yrs)	1.01 (0.97 to 1.05)	0.615	—	—
Illiterate	1.72 (0.84 to 3.55)	0.141	—	—
Did not permit home visits	0.79 (0.10 to 6.66)	0.141	—	—
HIV/AIDS status				
CD4 (cells/μL), categories				
<350	7.52 (1.71 to 33.02)	0.008	No ART: 11.86 (7.18 to 19.59)	<0.001
			On ART: 4.51 (1.08 to 18.84)	0.039
≥350	Reference	—	Reference	—
No CD4 result available	5.34 (1.10 to 25.93)	0.038	4.76 (1.63 to 13.93)	0.004
ART*	0.56 (0.25 to 1.26)	0.159	See above	—
Eligible for ART but not on ART*	2.85 (1.35 to 6.00)	0.006	—	—
Co-trimoxazole prophylaxis†	0.53 (0.25 to 1.09)	0.083	0.43 (0.12 to 1.66)	0.232
Vital signs				
Axillary temperature (°C)	1.24 (0.84 to 1.84)	0.284	—	—
Body mass index (kg/m^2) (6 missing)	0.80 (0.69 to 0.92)	0.002	0.92 (0.89 to 0.96)	<0.001
Hemoglobin				
Hemoglobin (g/dL) (2 missing)	0.70 (0.58 to 0.84)	<0.001	0.70 (0.58 to 0.85)	<0.001
Comorbidities‡				
Sexually transmitted infection (excluding pelvic inflammatory disease)	1.02 (0.22 to 4.81)	0.981	—	—
Oral candidiasis	2.68 (0.78 to 9.24)	0.118	—	—
Esophageal candidiasis (presumed)	6.03 (1.17 to 31.20)	0.032	6.59 (1.12 to 38.85)	0.037
Cutaneous mycosis	1.12 (0.13 to 9.92)	0.917	—	—
Symptoms				
Cough	1.10 (0.50 to 2.44)	0.809	—	—

Subject Characteristics at First Study Visit (n = 231 Subjects Who Improved, Died, or Were Hospitalized; Subjects With Unknown Outcomes Were Excluded)	Bivariate Associations With Death or Hospitalization (n = 231)		Multivariable Associations With Death or Hospitalization, Adjusted for Presumed Correlation of Outcomes Within Sites (n = 224)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Any upper respiratory symptom (sore throat, sneezing, congestion, ear pain)	0.87 (0.40 to 1.85)	0.711	—	—
Any lower respiratory symptom (dyspnea, chest pain, hemoptysis)	1.53 (0.68 to 3.46)	0.302	—	—
Any gastrointestinal symptom (nausea, vomiting, diarrhea, abdominal pain)	1.14 (0.54 to 2.40)	0.725	—	—
Any genitourinary symptom (discharge, dysuria, ulcer)	2.10 (0.96 to 4.59)	0.063	—	—
Headache	0.66 (0.27 to 1.58)	0.350	—	—
Skin problems	1.21 (0.30 to 4.48)	0.766	—	—
Weight loss	3.66 (1.75 to 7.68)	0.001	5.69 (2.22 to 14.56)	<0.001
Diagnoses/treatment at visit 1				
Malaria antigenemia	0.89 (0.32 to 2.46)	0.818	—	—
Slide-confirmed malaria parasitemia	0.79 (0.26 to 2.43)	0.685	—	—
Smear-positive TB (new diagnosis)‡	Undefined	—	—	—
Smear-negative TB (new diagnosis)	3.58 (0.82 to 15.72)	0.091	14.45 (1.43 to 146.42)	0.024
TB suspect§	2.91 (1.39 to 6.09)	0.005	—	—
Blood culture drawn at this visit detects bacteremia‖	2.87 (1.26 to 6.52)	0.012	Bacteremia, no antibiotics: 12.51 (2.21 to 70.86)	0.004
	—	—	Bacteremia, antibiotics: 0.71 (0.11 to 4.48)	0.719
Antibiotics prescribed‖	0.18 (0.08 to 0.42)	<0.001	Antibiotics, no bacteremia: 0.54 (0.30 to 1.00)	0.048
	—	—	No antibiotics, no bacteremia: reference	—
Antimalarials prescribed	0.72 (0.26 to 1.97)	0.518	—	—
Start TB treatment	5.73 (0.35 to 93.9)	0.221	—	—
Start antiretrovirals	0.41 (0.05 to 3.27)	0.403	—	—

*In multivariable model, ORs for association of CD4 category and outcomes are adjusted for interactions of CD4 <350 cells per microliter and ART.

†Retained in model because of a priori assumption that co-trimoxazole prophylaxis would be negatively associated with febrile illnesses.

‡New diagnosis for smear-positive TB dropped owing to zero cell sizes (no cases of hospitalization or death).

§Dropped from multivariable model because of collinearity.

‖In multivariable model, adjusted for interaction between blood culture results and antibiotic prescription at visit 1.